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10/588,685

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EXAMINER

MUMMERT, STEPHANIE KANE

ART UNIT

PAPER NUMBER

1637

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|---|-------------------------------------|--|
| Office Action Summary | Application No. 10/588,685 | Applicant(s) MODEL ET AL. | |
| | Examiner STEPHANIE K. MUMMERT | Art Unit 1637 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 September 2011.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 1,3-17 and 31 is/are pending in the application.
- 5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 1,3-17 and 31 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 12, 2011 has been entered.

Applicant's amendment filed on September 12, 2011 is acknowledged and has been entered. Claims 1, 3-17 and 31 have been amended. Claims 2, 18-30 and 32-39 have been canceled. Claims 1, 3-17 and 31 are pending.

Claims 1, 3-17 and 31 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL as necessitated by Amendment.

New Grounds of Rejection – adjusted to address amendment to the claims

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 9, 12, 14-15 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Fan et al. (US PgPub 20070269801; 102(e) date, December 3, 2002 or earlier).

With regard to claim 1, Fan teaches a method for producing non-methylated DNA, wherein a methylation analysis is used, comprising the steps of:

- a) performing a genome-wide amplification on genomic DNA, using non-methylated nucleotides or nucleotide triphosphates, thereby producing fully non-methylated DNA (Example 4, where the genome is amplified and methylation is analyzed; see paragraph 317-318 where the amplified genomic DNA serves as a fully unmethylated template);
- b) using the amplificates generated in a) as a non-methylated standard in the methylation analysis over a linear range (Example 4, where the amplified genomic DNA is used in calibration of methylation assays; see paragraphs 317-318 where unmethylated templates and methylated templates are mixed at known ratios).

With regard to claim 9, Fan teaches an embodiment of claim 1, further comprising using restriction enzymes (paragraph 77, where methylation sensitive restriction enzymes can be useful in methylation analysis).

Art Unit: 1637

With regard to claim 12, Fan teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by an amplification and a hybridization of the amplicates at oligomer microarrays (paragraph 220-225, where the methylation assay includes hybridization of amplification products on an array platform; see Figure 1 for example).

With regard to claim 14, Fan teaches an embodiment of claim 1 wherein a mixture of methylated and non-methylated DNA is used as a standard (see paragraphs 317-318 where unmethylated templates and methylated templates are mixed at known ratios).

With regard to claim 15, Fan teaches an embodiment of claim 1 wherein several mixtures of methylated and non-methylated DNA with different shares of methylated and non-methylated DNA are used as a standard (see paragraphs 317-318 where unmethylated templates and methylated templates are mixed at known ratios).

With regard to claim 31, Fan teaches an embodiment of claim 1, wherein the genome-wide amplification is performed by exclusively using nucleotides or nucleotide triphosphates, respectively, which are non-methylated (Example 4, where the genome is amplified and methylation is analyzed; see paragraph 317-318 where the amplified genomic DNA serves as a fully unmethylated template).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1637

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan as applied to claims 1, 9, 12, 14-15 and 31 above and further in view of Mamone et al. (Genomic/Proteomic Technology, April/May 2003).

With regard to claim 5, Fan teaches an embodiment of claim 4, further comprising using a phi 29 polymerase (Example 4, paragraph 317-318 where amplification can be carried out using any techniques for whole genome amplification, including phi29 polymerase amplification).

With regard to claim 6, Fan teaches an embodiment of claim 4, further comprising using a commercially available kit (Example 4, paragraph 317-318 where amplification can be carried out using any techniques for whole genome amplification, including phi29 polymerase amplification or OmniPlex technology in kit form).

Regarding claim 4, while Fan teaches the use of phi29 polymerase, Fan does not specify that the amplification is achieved by multiple displacement amplification.

With regard to claim 4, Mamone teaches an embodiment of claim 1, wherein the amplification method performed is a multiple displacement amplification (MDA) (Abstract, Figure 1, where the method comprises multiple displacement amplification using GenomiPhi).

With regard to claim 7, Mamone teaches wherein the commercially available kits are GenomiPhi or Repli-G (Abstract, Figure 1, where the method comprises multiple displacement amplification using GenomiPhi).

Art Unit: 1637

With regard to claim 8, Mamone teaches using a commercially available DNA produced by MDA used as a standard (Abstract, Figure 1, where the method comprises multiple displacement amplification using GenomiPhi).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Fan to include the specific whole genome amplification technique of multiple displacement amplification (MDA) as taught by Mamone to arrive at the claimed invention with a reasonable expectation for success. As taught by Mamone, “one way the amplified product is not representative of genomic DNA is that epigenetic information is lost. There is no known way to recover methylation pattern data from DNA synthesized by this method” (p. 3, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Fan to include the specific whole genome amplification technique of multiple displacement amplification (MDA) as taught by Mamone to arrive at the claimed invention with a reasonable expectation for success.

Claims 3, 10-11, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan as applied to claims 1, 9, 12, 14-15 and 31 above and further in view of Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622).

With regard to claim 3, Wong teaches an embodiment of claim 1 wherein the amplification methods performed are PEP, DOP-PCR or linker PCR (p. 2619, col. 2, where whole genome amplification was carried out with PEP amplification, p. 2620, col. 1).

Art Unit: 1637

With regard to claim 10, Wong teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by methylation- specific ligation methods, MSP, Heavy Methyl or MethyLight (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction, p. 2620. col. 1, where methylation specific PCR is described, see Figure 1).

With regard to claim 11, Wong teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by primer extension (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction, p. 2620. col. 1, where methylation specific PCR is described, see Figure 1).

With regard to claim 16, Wong teaches an embodiment of claim 1 wherein the methylation analysis is performed for the diagnosis of cancer diseases or other diseases associated with a modification of the methylation status (Abstract, Figure 1, Table 1, where the technique was used to detect methylation in cancer samples).

With regard to claim 17, Wong teaches an embodiment of claim 1 wherein the methylation analysis is performed for the prognosis of desired or undesired effects of drugs and for the differentiation of cell types or tissues, or for the investigation of the cell differentiation (Abstract, Figure 1, Table 1, where the technique was used to detect methylation in cancer samples).

Art Unit: 1637

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Fan to include the additional whole genome amplification techniques of Wong to arrive at the claimed invention with a reasonable expectation for success. As taught by Wong, “we now report the ability to reduce the amount of DNA necessary for the assay at least 60-fold with PEP, a PCR based method for whole genome amplification using a mixture of degenerate 15-base oligonucleotide primers” (p. 2619, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Fan to include the additional whole genome amplification techniques of Wong to arrive at the claimed invention with a reasonable expectation for success.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fan et al. (US PgPub 20070269801; 102(e) date, December 3, 2002 or earlier) as applied to claims 1, 9, 12, 14-15 and 31 above and further in view of Tost et al. (Nucleic Acids Research, 2003, 31(9):e50, p. 1-10).

With regard to claim 13, Tost teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by means of a multiplex PCR (p. 6, col. 2, where the CpG methylation was detected using multiplex primer extension).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Fan to include the analysis of methylation

Art Unit: 1637

using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success. As taught by Tost, "Calibration curves were recorded for simplex, duplex and triplex analysis. For multiplex analysis only extension primers were chosen that did not overlap in their sequence". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Fan to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success.

Citation of Pertinent Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dean et al. (US Patent 6,617,137 September 2003) teaches methods of whole genome amplification.

Response to Arguments

Applicant's arguments with respect to claims 1, 3-17 and 31 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

Art Unit: 1637

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Primary Examiner, Art Unit 1637

SKM